# Rett Syndrome—An Early Catecholamine and Indolamine Deficient Disorder?

Yoshiko Nomura, MD, Masaya Segawa, MD
and Makoto Higurashi, MD

*The results of clinical and polysomnographical examinations on 11 Japanese Rett syndrome cases were summarized to substantiate further our previous results regarding the pathophysiology of the disease.*

*It was concluded that the disease starts early in infancy and takes a progressive course. Each characteristic symptom appears in an orderly sequence which is thought to reflect the sequential systemic involvement of certain neuronal systems. Based on the characteristic symptoms and signs, and polysomnographical studies, we speculated that the initial lesion was the locus coeruleus with a hypoactive noradrenergic system combined with other hypoactive monoaminergic systems, including those of serotonin and dopamine, occurring along with the early developmental course. In later stages, hyperfunction possibly due to postsynaptic supersensitivity of the dopamine system causes the characteristic symptoms of the Rett syndrome.*

*Nomura Y, Segawa M, Higurashi M. Rett syndrome – an early catecholamine and indolamine deficient disorder? Brain Dev 1985; 7:334-41*

The Rett syndrome is a specific disorder of psychomotor developmental delay, behavioral problems and motor disturbances comprising an unique disease entity [1-3].

Detailed clinical studies on our initial 5 patients were reported previously together with a brief presentation of 6 other cases [3]. This paper reports the summary and the confirmation of the clinical characteristics of the Rett syndrome, and speculates further on the pathophysiology basing on the results of polysomnographical examinations. Preliminary results of the therapeutic trials are also presented.

From the Segawa Neurological Clinic for Children, Tokyo (YN, MS); Department of Health Sciences, Yamanashi Medical College, Nakakoma, Yamanashi (MH).

*Key words: Rett syndrome, catecholamine and indolamine deficiency, 5-HTP, L-Dopa, L-threo-3,4-dihydroxyphenylserine, polysomnographical studies.*

Correspondence address: Dr. Yoshiko Nomura, Segawa Neurological Clinic for Children, 2-8 Surugadai Kanda, Chiyoda-ku, Tokyo 101, Japan.

## Materials and Methods

Eleven patients who ranged in age from 3 to 14 yrs and were all female, were followed for 6 mos to 11 yrs 9 mos.

Neurological examinations were performed repeatedly during the follow-up period. For all patients, various laboratory examinations and electrophysiological and radiological evaluations were performed.

All night polysomnographical examinations were performed on 7 patients, in one case three tests were performed before and after L-threo-3,4-dihydroxyphenylserine (DOPS) treatment. Besides EEG, EOG and surface EMG of the mentalis muscles, the EMG activities of the sternocleidomastoid, rectus abdominalis and 8 muscles of the bilateral extremities were recorded with surface electrodes to analyze the body movements. Two types of body movements were evaluated; gross movement (GM)—diffuse sequential muscle activities including those of the rectus abdominalis and lasting more than 2 seconds, and twitch movement (TM)—short muscle activities localized to one muscle and lasting less than 0.5 seconds. The number of TM of the mentalis muscle during the REM stage (ment TM REM) and the num-

ber of rapid eye movements (REMs) were counted, and the ratio of ment TM REM against REMs (ment TM REM/REMs) was calculated.

Based on our working hypothesis on the pathogenesis of the Rett syndrome [3] that primarily the raphe nuclei and locus coeruleus are involved initially followed by the basal ganglia, a therapeutic trial with precursors of neurotransmitters of these nuclei, 5-HTP, DOPS and L-Dopa was performed.

## Results

### *1. Clinical Characteristics*

The major motor milestones are presented in Table 1 and Fig 1. Three showed a delay in head control and all showed a delay in attaining motor milestones of the mid and later parts of infancy, such as rolling over, sitting and crawling. Standing and walking with or without support were delayed in all except two who attained these activities at normal ages but crawling was delayed and difficult. Maximum motor achievements ranged from sitting to running.

During the course, regression of the major motor activities was seen. This became apparent around the middle of the first decade with varying severity, however, the subtle signs of regression appeared by the age of 3 yrs and in most patients with difficulty getting up from the lying position.

The head circumference at birth was within normal limits except for one case in which it was slightly smaller than the mean−2SD but it began to taper down in all cases in late infancy (Fig 1).

Behavioral abnormalities became apparent in all patients from early infancy and the characteristic autistic traits of this age were seen. The autistic features characteristic of before and after 1 yr of age were evaluated in 9 cases. Most of the patients showed the autistic symptoms of infancy but those of early childhood were less prominent suggesting that they were masked by the overlaying severe mental retardation (Fig 2).

The most characteristic hand washing like stereotyped movements showed some variation with age and among individuals. These features of stereotyped movements suggested to be involuntary in nature and a certain neuronal circuit is probably responsible for the pathophysiology [3].

Purposeful hand use was lost before the stereotyped movements of the hand began.

Besides this, there were other types of involuntary movements, such as teeth grinding, tongue protrusion, licking and dyskinetic movement around the mouth.

Shivering or tremulous movement of the whole body with or without hyperventilation was seen in some patients.

The gait was also characteristic, being broad

Table 1 *Major motor milestones in the 11 cases*

| | *Age* | *Head control* | *Rolling over* | *Sitting when placed* | *Sitting by themselves* | *Crawling* | *Standing with support* | *Standing without support* | *Walking with support* | *Walking without support* |
|---|---|---|---|---|---|---|---|---|---|---|
| I | 4y 10m | 2m | 7m | 8 m | – | 1y 4m | – | – | 10m | 1y 4m |
| II | 7y 3m | 5m | – | – | 3y | 1y 1m | 1y 3m | 5y 1m | 1y 5m | never |
| III | 7y 11m | 3m | 8m | 8 m | – | 1y 1m | 2y 5m | 4y 10m | 3y | 4y 11m |
| IV | 11y 4m | 10m | – | – | – | 1y 1m* | 2y | never | never | never |
| V | 14y | 4m | 10m | 7 m | 1y | 1y 3m | 1y 6m | 4y | 2y 3m | 5y 4m |
| VI | 3y | 3m | 7m | 9 m? | 9m | 11m | 1y 6m | 1y 7m | 1y 6m | 1y 9m |
| VII | 4y 5m | 2m | 6m | 6 m | – | 11m | 9m | 1y 3m | 9m | 1y 3m |
| VIII | 4y 3m | 3m | 10m | 8.5m | – | 11m | 1y 2m | – | 1y 4m | 1y 7m |
| IX | 4y 4m | 5m | 7m | 1y | – | 10m (+backward) | 3y | never | never | never |
| X | 9y 9m | (3m) | – | 7 m | – | – | – | – | – | 1y 11m |
| XI | 10y 6m | 3m | 1y 2m | 6 m | – | never | never | never | never | never |

*: at 1 yr 5 mos, shuffled backwards, –: not known.

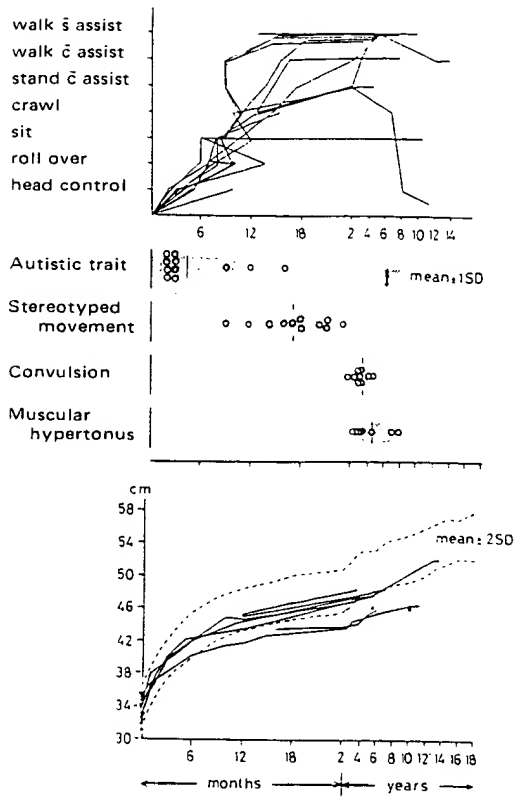


Fig 1 *Motor milestones, main symptoms and head circumference, Abscissa: age.*

based with short steps and lack of coordinated movement of the upper extremities. Another important point is that crawling was very difficult with all.

Initiation of both crawling and walking was more affected, but passive or voluntary applied rhythmic rolling movements of the trunk improved this.

The most important feature of the Rett syndrome is that the symptoms occur in an orderly sequence at certain ages [3]. The mean age ± 1 SD of the main symptoms in the 11 patients were as follows: autistic traits at 4.6 mos ± 6.6 mos, stereotyped hand movements at 1 yr 5 mos ± 4.2 mos, convulsions at 3 yrs 5 mos ± 10.5 mos and muscle hypertonus at 4 yrs 6 mos ± 2 yrs 4 mos (Fig 1).

This age dependent appearance of the symptoms and delay in the major milestones of the 11 patients were correlated to the decremental change in the head circumference (Fig 1).

### 2. *Polysomnographical Examinations (PSG)*

Our previous evaluation of 4 patients [3] were further substantiated with 7 patients including the previous 4. Among these, the results of 5 including the previous 3 are presented.

As for the sleep structure, the cyclic occur-

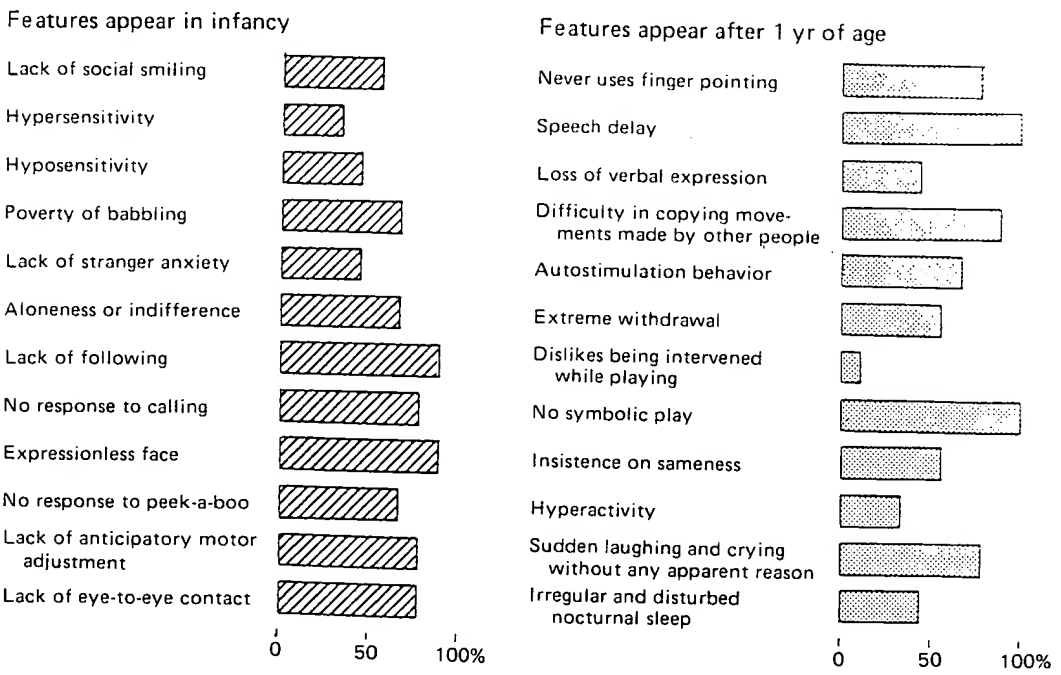


Fig 2 *Autistic traits in Rett syndrome – 9 cases.* ▨ ▭ : % of the presence of the each symptom.

rence of stage REM and prolongation of its period in later sleep stages were observed normally. However, slow wave sleep occurred in the second half of sleep in all cases (Fig 3).

Percent-sleep-stages revealed a relatively greater stage REM in older patients (Fig 4).

As for the motor components, abnormalities were observed in both the tonic and phasic components, that is, the tone of the mentalis muscle was lost even during non-REM sleep (Fig 3).

The number of GM per hour against sleep stages revealed to be abnormally low in stage REM in older patients showing abnormality in the pattern (Fig 5).

The modulation of the number of TM against sleep stages revealed a normal pattern but the number was abnormally increased in

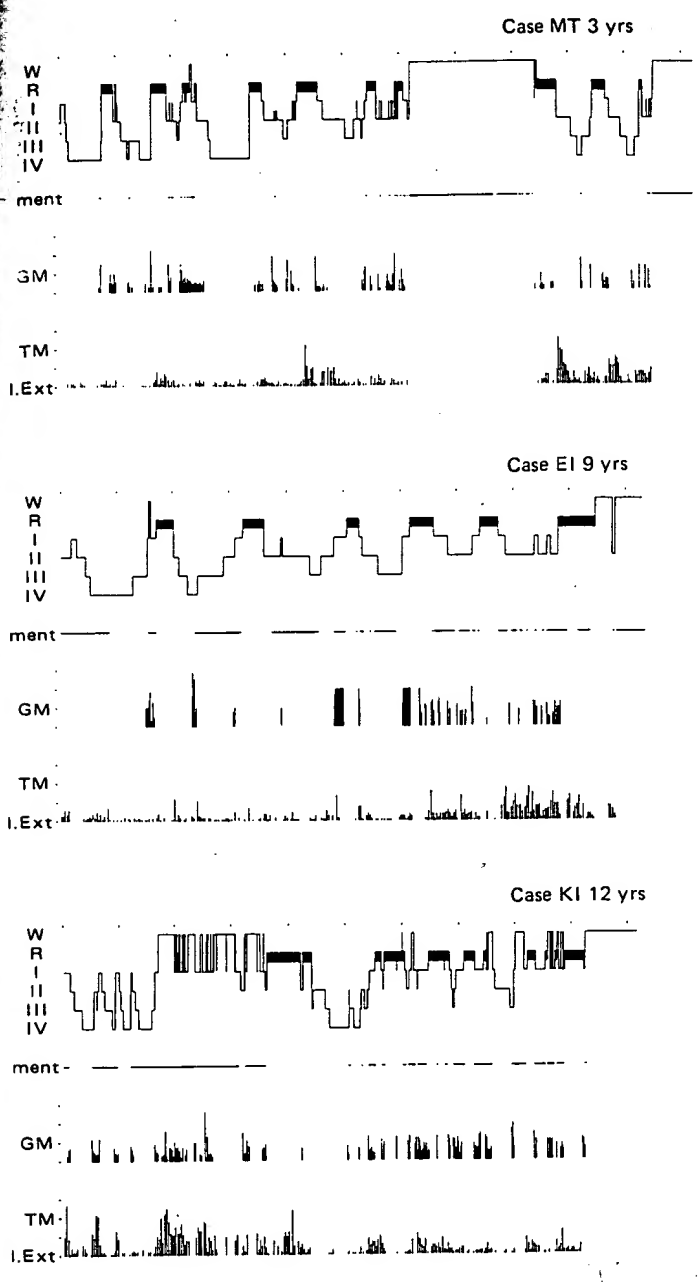


Fig 3 *Sleep diagrams of three cases. Horizontal line in the ment section represents the presence of mentalis muscle tone. Vertical line in the GM section represents the duration of each GM. Vertical line in the TM section represents the number of TM.*

all sleep stages. These features were marked in the upper extremities and more prominent on the right than the left, and in the lower extremities the number of TM was normal except for the youngest case, aged 2 yrs 7 mos (Fig 6).

The ment TM REM/REMs showed abnormally high values in advanced older patients, but were within normal limits in younger cases (Fig 7).

Day-by-day plot of the sleep and wakefulness cycle revealed an irregular sleep onset time and relatively longer daytime sleep (Fig 8), as observed before [3].

### 3. *Therapeutic Trials*

5-HTP was tried in 5 cases and has been continued for 1 yr 5 mos to 1 yr 8 mos. Improvement of the sleep onset time and autistic behavior was suggested. One young patient was suggested to show improvement in coordinated movements. Two patients were placed

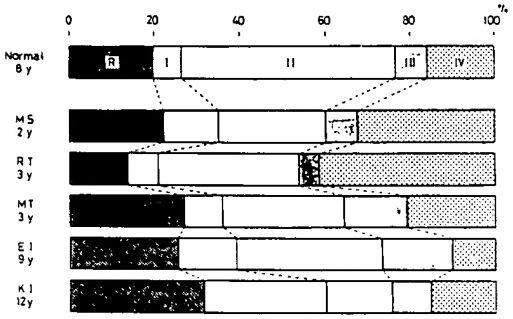


Fig 4 *%-sleep-stages.*

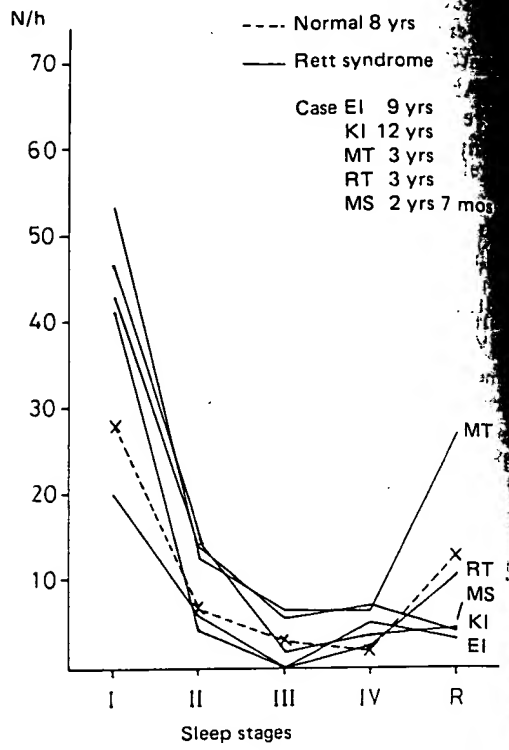


Fig 5 *Gross movement against sleep stages. Each line represents one patient.*

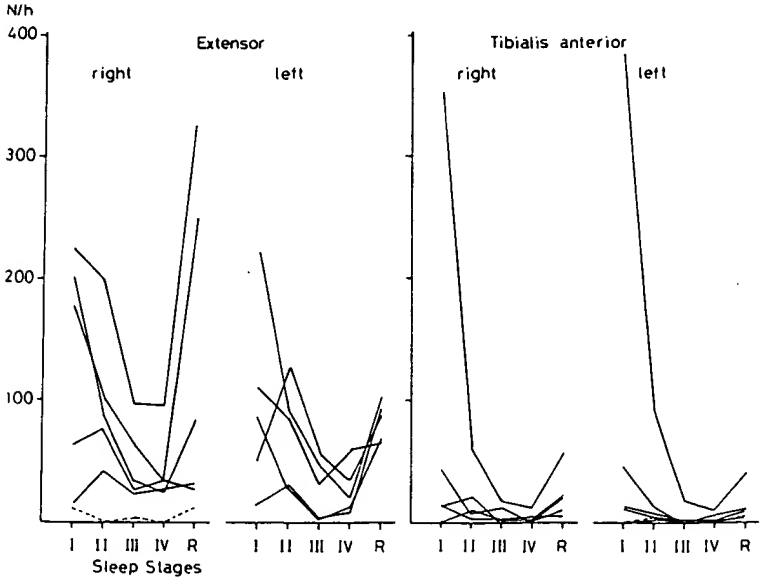


Fig 6 *Twitch movement against sleep stages. Each line represents one patient.*
*--------: normal, 8 yrs.*

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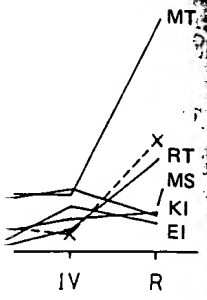
Normal 8 yrs
Rett syndrome

Case EI 9 yrs
KI 12 yrs
MT 3 yrs
RT 3 yrs
MS 2 yrs 7 mos

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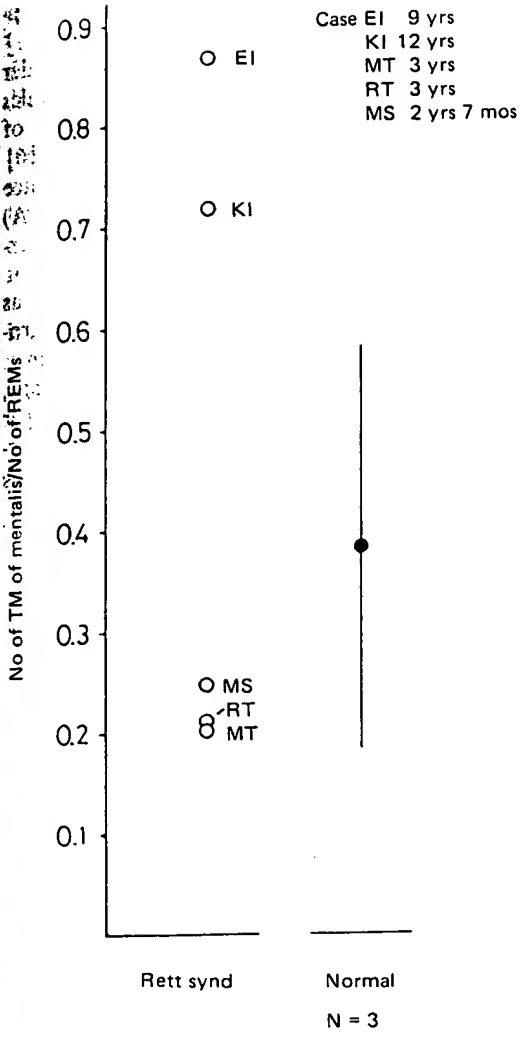


Fig 7 *Ratio of twitch movements of mentalis muscles against rapid eye movements in stage REM.*

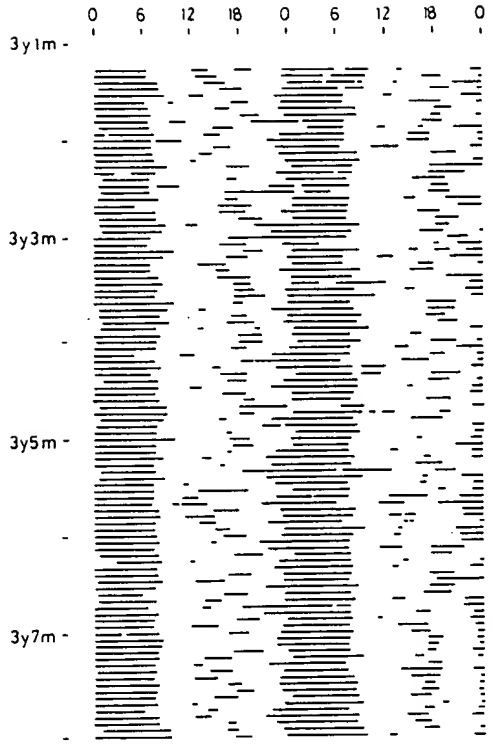


Fig 8 *Circadian oscillation, Case NT. Abscissa: time (o'clock), Ordinate: age, ——— : sleeping state.*

5-HTP for only 1 mo without any change.

L-Dopa was tried in 4 patients for 8 mos to 3 yrs 1 mo. One showed a slight increase in stereotyped hand movement and developed screaming. There has been no appreciable improvement in muscle hypertonus.

DOPS has been tried on the youngest case for 4 mos from the age of 3 yrs 2 mos. Clinical changes revealed that she began to take the on-the-four posture and to crawl.

PSG was performed 3 times for this patient at ages 2 yrs 7 mos and 3 yrs 2 mos before the DOPS treatment and thirdly during DOPS treatment. Percent-sleep-stages revealed no significant differences. The position of REM and slow wave sleep and prolongation of REM in later sleep cycles remained normal without alteration. There was no appreciable change in GM, however, TM showed a tendency to decrease towards the normal level in the upper extremities.

### *4. Genetic Evaluation*

To evaluate the female gynecotrophy of the Rett syndrome, we tried to investigate the sex ratio in the families of affected girls and to examine the high resolution banding on X-chromosomes of the affected cases.

The sex ratio in the sibs of 10 propositi was 5 males:6 females or 0.83, which is slightly lower than the expected ratio. The sex ratio in the cousins of 9 propositi was 35 males:30 females or 1.17.

The incidence of spontaneous abortion in the sibs of the 10 propositi was only one.

From these limited data, it is difficult to say whether the sex ratio in the sibs was significantly lower.

High resolution banding patterns of X-chromosomes in 2 cases revealed no particular abnormality.

## Discussion

Our clinical evaluation revealed that the symptoms of the autistic tendency started very early and the developmental delay was often present before the characteristic symptoms started, furthermore, there was an early decrementation of head circumference. These facts suggest that the underlying pathologies start early in infancy.

The progressive course observed in the developmental decrease and the regressive course suggest that the disease is progressive and degenerative, and the parallel changes in the clinical features and head circumference suggest this is a disease involving a broad system as it progresses.

Thus the very early onset of the symptoms followed by the orderly sequential occurrence of specific symptoms made us speculate that the initial lesion to be in the lower CNS, either in the brainstem and/or midbrain which matures early in infancy and gives a broader influence during development on a particular region of the higher CNS.

Thus, sequential involvement of the higher levels of particular nervous systems which are influenced by the lower brain structures would cause the characteristic age related symptoms of the Rett syndrome [3].

Based on the clinical features and results of behavioral animal experiments, specific brainstem nuclei and basal ganglia were speculated to play important roles in the pathophysiology. By analyzing each symptom, we speculated that the raphe, locus coeruleus and dopamine system in the basal ganglia were involved [3].

Then which nuclei in the brainstem or midbrain could be the initial lesion? There are substantial evidences indicating the close correlations between certain nuclei in the brainstem and midbrain, and sleep parameters [4].

The abnormal tonic components of sleep with disturbance of the position of slow wave sleep and loss of tonic activities of the mentalis muscle suggested the involvement of the locus coeruleus. The progressive increase in percentstage REM and increase in the TM with age suggested that the process reversed the developmental course.

The results of the TM as well as GM in older cases are similar to our previous study of Gilles de la Tourette syndrome [5] and a case of tuberous sclerosis with rotatory seizures [6] which was thought to be due to the presence of hyperfunction of the dopaminergic (DA) system, probably due to postsynaptic supersensitivity [5, 6].

The ratio of ment TM REM/REMs was thought to reflect the activity of the nigrostriatal DA neurons [7]. In the Rett syndrome, this ratio increased progressively with age, though it was within normal limits in younger patients. These features also suggest a progressive increase in the activity of the DA neurons in this syndrome.

These results on the phasic components of sleep parameters could be interpreted as the developing postsynaptic supersensitivity of the DA neurons, but it could also be explained alternatively as developing hyperactivity of DA neurons due to prolonged disinhibition of the neurons by hypofunctioning serotonin (5HT) or noradrenaline neurons.

The abnormal circadian rhythm can occur with raphe and locus coeruleus leions [8, 9].

Based on the results of clinical analysis of the characteristic symptoms and sleep studies, our hypothesis for the pathophysiology of the Rett syndrome is as follows:

The earliest lesion is hypoactivity either in the raphe and/or locus coeruleus causing the autistic trait in early infancy.

As the disease progresses, the DA system becomes hyperactive due to postsynaptic supersensitivity caused by hypoactive 5HT neurons or to disinhibition of the neurons by affected 5HT or noradrenaline neurons, which leads to the characteristic motor symptoms especially the stereotyped movements.

We reported that the pathophysiology of the characteristic gait seen in the Rett syndrome was akinesia rather than apraxia [3]. Narabayashi et al demonstrated that the basis of the akinesia was related to the hypofunction of noradrenaline [10]. So the hypofunction of noradrenaline could be responsible for the specific gait seen in this disease.

Recently, Brenner et al demonstrated the impaired growth of the cerebral cortex of rats treated neonatally with 6-hydroxydopamine

with low noradrenaline in the cerebral cortex [11]. Could this be applied as the basis for the progressive microcephalus in the Rett syndrome?

It is known from animal experiments that the serotonergic system as well as the noradrenaline system are the systems which are influenced by environmental factors but the serotonergic system is more susceptible in males [8].

So in the Rett syndrome which occurs only in females, the noradrenaline system rather than the serotonergic system might be primarily deficient.

This hypothesis for the pathophysiology of the Rett syndrome has to be examined further, pathologically, histochemically and biochemically.

Our efforts to treat this disease by replacing 5-HTP, DOPS and L-Dopa, based on our hypothesis, is only preliminary, however, improvement of crawling and the TM pattern in PSG after DOPS treatment is attractive for further follow-up.

As for the female gynecopathy, it is consistent with previous reports [1–3] that all our cases were females. The confinement of this syndrome to girls in all cases still remains puzzling. The hypothesis that the transmission pattern of this syndrome may be an X-linked dominant mutation lethal for males is very difficult to confirm because affected girls are unlikely to bear children. Further evaluation of the X-chromosome including fragile X would be rewarding.

**Acknowledgments**

The authors thank the many young colleagues at the Segawa Neurological Clinic for Children for their assistance in the clinical evaluation and Ms Anna Benis for her secretarial work.

**References**

1. Rett A. Cerebral atrophy associated with hyperammonaemia. In: Vinken PJ, Bruyn GW, eds. *Handbook of clinical neurology*. Vol 29. Amsterdam: North Holland Publ Co, 1977:305-29.
2. Hagberg B, Aicardi J, Dias K, Ramos O. A progressive syndrome of autism, dementia, ataxia and loss of purposeful hand use in girls: report of 35 cases. *Ann Neurol* 1983;14:471-9.
3. Nomura Y, Segawa M, Hasegawa M. Rett syndrome – Clinical studies and pathophysiological consideration. *Brain Dev (Tokyo)* 1984;6:475-86.
4. Segawa M. Sleep mechanism and its development (in Japanese). *Pediatrics (Tokyo)* 1980;21:441-53.
5. Nomura Y. Tics (Gilles de la Tourette syndrome) (in Japanese). *Adv Neurol Sci (Tokyo)* 1985;29:265-75.
6. Tanaka S, Igawa C, Ogiso M, Nomura Y, Segawa M. Epileptic seizure with rotational behavior in tuberous sclerosis. *Folia Psychiatr Neurol Jpn* 1983;37:331-2.
7. Segawa M, Nomura Y, Kase M. Dystonia of childhood. The roles of the dopaminergic system – Clinical and polysomnographical studies. To be published.
8. Segawa M. Early infantile autism (in Japanese). *Jpn J Neuropsychopharmacol (Tokyo)* 1979;1:189-200.
9. Okawa M, Sasaki H. Disorders of sleep-waking rhythm – A report of three cases (in Japanese). *Adv Neurol Sci (Tokyo)* 1981;25:1164-75.
10. Narabayashi H, Kondo T, Hayashi A, Suzuki T, Nagatsu T. L-threo-3,4-dihydroxyphenylserine treatment for akinesia and freezing of parkinsonism. *Pro Japan Acad Ser B (Tokyo)* 1981;57(B):351-4.
11. Brenner E, Mirmiran M. Uylings HBM, Van Der Gugten J. Impaired growth of the cerebral cortex of rats treated neonatally with 6-hydroxydopamine under different environmental conditions. *Neuroscience Letters* 1983;42:13-7.